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ABSTRACT

There are three phases in the development of new drugs aimed at determining adverse reactions or side effects. Each of these phases produces many different pieces of information. All of this leads to a major problem involving the professional/industrial and/or academic libraries serving the scientific-medical community through their information centers. The major components of this problem are definition of adverse reactions, their collection, classification, storage and retrieval. The objective of this report is to lend insight into this complex area and to direct suggestions to the information scientists who may assist the clinicians involved in medication selection. (Author/SJ)

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THE HISTORY, SCOPE AND PLAN FOR AN INFORMATION CENTER SERVICE

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In the process of drug development, one of the primary concerns of the clinical investigator, the originating pharmaceutical company and the government bureau involved has been the occurrence of adverse reactions, which are sometimes referred to as side effects.

When a new drug (a new chemical entity or combination of two or more other drugs) is being evaluated, the first step is designed for the purpose of determining possible reactions to the drug and of increasing the dose to that point where an adverse or toxic effect may be observed. This determination is derived from the patient's subjective description and from the many laboratory parameters which are computed (blood chemistries, urinalysis, complete blood count, serum electrolytes, X-rays, electrocardiograms, electroencephalograms, etc.). This information on the drug's action is hoped to be positive, but when an adverse reaction occurs, the clinician must learn to classify the reaction into one of two major groups: either drug related or not drug related. This first step is relatively easy, because of the ability to measure the severity of the reaction against the dosage at which it appeared and because the investigator can balance those reactions occurring in the medicated group with those occurring in the control, or reference group, which consists of subjects taking either placebo or a known drug. At all times during the process of drug evaluation with the exception of testing for safety, the experimental design is double-blind to insure valid results, and statistical analysis of the data derived is utilized to evaluate signiiicance. All efforts are made to introduce a minimal number of variables and a random population homogenous in its

characteristics.

However, the problem of drug evaluation and development becomes more complex as the patient's diagnoses and history and the influence of concomitant medications are taken into consideration, and as the development continues into the second of its three phases. Phase I, which is discussed above, is usually carried out in normal healthy volunteers, and then in patients whose particular disease is to be treated by the drug in question. This use of normals and patients is an important consideration, as medications act differently in all people and have been known to effect normal volunteers differently than those people who will be taking it as therapy.

Phase II is a developmental stage designed to pinpoint and expand the understanding of the mechanism of action of the drug and its effect in treating a particular diagnosis. Finally, Phase III is a large-scale and wide-spread testing program throughout the country, so that the influences of different climates and psychological personalities are taken into consideration.

Throughout this timely and expensive process many new pieces of information are collected, such as facts about the compound in question, about the disease entity being studied, about patient vulnerability to interaction of drugs given concomitantly and about interaction of diagnoses.

All of this leads to a major problem involving the professional/industrial and/or academic libraries servicing the scientific-medical community through their information centers. The major components of this problem are definition of adverse reactions, their collection, classification, storage

and retrieval. The objective of this discourse is to lend insight into this complex area and perhaps to direct some suggestions to the information scientists who may assist the clinicians intimately involved in medication selection.

This problem has attracted much publicity over the last 5 to 8 years due to a wealth of literature that has come from the profession, but of even greater consequence has been the coverage given to it in the lay press. The Thalidomide scare brought public attention to the problem. Although all people are contributing factors to adverse reactions, only the most sophisticated were previously aware of it. With Thalidomide people became cautious of medication - any and all "pills". The press did not inform the masses that Thalidomide was and is an excellent sedative and if used properly (in the right population) it is safe and efficacious. However, in the hands of expectant mothers it could cause (in less than 1%) phocomelia. An interesting finding that has never been proven was that 50% or more of those women who gave birth to deformed children were either pregnant out of wedlock or the pregnancy was unwanted; thereby introducing a negative psychological component which may have contributed to this physiological phenomenon. Thalidomide is used overseas in sanitoriums where female patients will not become pregnant. No adverse effects have ever been found in males taking the medication.

Another example of adverse effects which have received public attention are those occurring in females taking contraceptive medications. The side effect most frequently observed is that of blood clots which travel to some

vulnerable spot in the body causing thrombosis which has been blamed for many deaths. In this instance there has not been sufficient statistical evidence to back these claims and there are many women still safely using the medication. Again, the lay press have detailed so many side effects that may occur that women fear taking the medication and those on the drug have often, through power of suggestion, manifested adverse reactions.

Adverse drug reactions are an international problem in which many world-wide agencies have taken an interest. The World Health Organization's International Drug Monitoring Project under Dr. Jan Venulet has cooperated with many countries through their drug regulatory agencies: Drug Advisory Bureau , Food and Drug Directorate of Canada - Dr. Jeffery Bishop; The United States Food and Drug Administration's Center for Drug Information - Dr. Arthur Ruskin; Scotland's Medicines Commission - Sir Derrick Dunlop; and England's Dunlop Committee - Dr. D. Mansel-Janes, Principle Medical Officer, Committee on Safety of Drugs, as well as others.

The history of adverse reaction collections started with the American Medical Association which collected reports of side effects to particular products but did not take into consideration the incidence of each effect. The Food and Drug Administration (FDA) has always acted as a depot for reaction reports, but no formal action was ever taken until a collection system was initiated in the 1950's and continual surveillance started in the 60's. In 1963 the FDA started a Hospital Reporting Program with some 200 hospitals participating. However, not until 1965 were computers utilized and an adverse reaction dictionary compiled which made further advances

possible.

Additional work was done by Dr. Leighton Cluff and his associates at Johns Hopkins Hospital[43] on the epidemiology of adverse drug reactions. One of his main findings showed a direct correlation of reaction rate, mortality and duration of hospital stay with the number of drugs administered (45% reaction rate in those patients taking 21 or more drugs). Therefore, providing evidence that multiple administration can very substantially increase the likelihood of reactions.

The National Library of Medicine also became involved in the collection of adverse reaction reports but only from published sources. The National Library of Medicine established the Medical Literature Analysis and Retrieval System (MEDLARS). They have an excellent up-to-date collection of published literature but this does not break down the material into raw data.

On local levels, the Drug Reaction Registry in Philadelphia attempted to coordinate adverse reactions in the early 60's.

In setting up an International Drug Surveillance Center as suggested by the Drug Research Board of the National Academy of Sciences - National Research Council [37], the first problem will be one of definition; for example the FDA's[34] definition has been, "Any substantiated noxious-pathologic and unintended change in the structure, functions and chemistry of the body that is not a part of the disease and is linked with any substance used in the prophylaxis, diagnosis or therapy of disease or for the modification of the physiologic state."

The Philadelphia Registry's meaning was, "A response to a drug that was

unintended and undesired by the physician who prescribed it and which was severe enough to be commented upon in the progress notes."

Dr. Cluff defined an adverse reaction as, "a response to a drug that was unintended and undesired by the physician who prescribed it."

The World Health Organization's definition is a reaction that, "is noxious, unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."

The Canadian Food and Drug Directorate defines a drug reaction as, "one which is of neither therapeutic, prophylactic nor diagnostic benefit to the patient."

These definitions raise many questions:

1. What are any effects not expected? Should it occur or is it unintended?
2. What are any effects not expected by the physician - does this then become a subjective analysis?
3. Any effects not expected at normal doses - what is a normal dose? What about voluntary or involuntary overdoses?
4. What is a substantial effect?
5. What is severe enough?
6. What is a normal dose for a particular individual?

Dr. Jan Koch-Weser, Chief of the Clinical Pharmacology Unit at Massachusetts General Hospital summarizes the problem as:(34)

"1. Only those drug-induced undesirable events which have a bearing on the significant risk of the appropriate use of drugs should be termed adverse reactions....."

"2. Degree of certainty of a drug-adverse reaction cause-effect relationship should not be required to be high....."

"3. In addition to a description site*, manifestation and, if known, mechanism,

*area effected

each adverse reaction should be characterized in terms of its significance to the patient's course...."

The problem is therefore "clearly" presented --- what information do we deal with and how? A glossary of terms could be developed based on statistically significant relationships and correlations of information on pharmacological effects to adverse reactions and drug interactions. This would initiate a common language which should be adhered to strictly so that computer based central filing systems could be maintained.

The development of the program with the cooperation of the entire biomedical profession would benefit everyone. The recent International Conference on Adverse Reaction Reporting Systems[37] has proposed a National Drug Surveillance Center, and from this there could develop a computer-based storage and retrieval depot. This center could act as an international information analysis institute. Then, once the system is fully operational, terminals could be placed in large medical centers and clinics and at pharmaceutical companies so that data can be easily and rapidly retrieved.

If the main obstacle can be overcome, namely, defining the term adverse reaction, the programming can easily be worked out utilizing many of the specialized clinical data collection systems[5,6,7,16,17] which are currently in use. For example, computerized electrocardiogram findings [23], computer readable surgical pathology[30], the computerized electroencephlogram findings or the program for determining dosage schedules for cardiac glycosides. From these programs and many others an indexing system can be initiated for

collection of clinical data.

It has also been proposed by the recent international conference that the surveillance center be authorized to take collected raw data and set up special epidemiological studies to update correlations and interactions. With the help of information science personnel this raw data could be analyzed and repackaged so that only current information would be disseminated. T.C. Gams[13] pointed out in reference to medical instrumentation, and this is applicable to clinical data, that all raw data should be collected regardless of significance. It could then be "ordered" into accessible and identifiable data and then "compressed" into significant data which can be based on fixed or arbitrary limits. This information can then be interpreted and classified for retrieval.

The ultimate goal would be for all pharmaceutical companies to enter their basic data (chemical, biological and clinical) on compounds as they are approved by the FDA. Then as the drug is prescribed the physicians would submit their data. This information could then be analyzed along with all other compounds already in the system. In this manner everyone interested could retrieve information for better prescription writing or for further research use. This procedure demonstrates a flow of information from the originator through the prescriber to the user.

To retrace our steps, we should consider the sources of information that are now available to the practicing physician who does not have time to keep up with the current masses of literature. He is dependent on mailings, advertising, detailing and the "package insert" that is required to be in all

medication packaging. This package insert, also compiled into a text called the Physician's Desk Reference, must be cleared by the government for content (indications, contra-indications, precautions, dosage and routes of administration) but this is not complete or total information. Many medical librarians are unaware of these sources of data and feel that the library is still the main outlet. From a legal standpoint the physician is not bound by this literature. Don Harper Mills, M.D., J.D.[34] in a presentation at the Drug Information Association Symposium on Adverse Reactions stated: "Package inserts do not set the standard of practice for drug use; the information contained therein constitutes only one of many factors for physicians to consider when prescribing drugs."

Therefore, in order to have quick recall of pertinent information there should be a method of retrieval available to every medical practice. This would be the ultimate goal and not one that far removed, as all medical technology today is working toward a computerized diagnostic procedure to assist the physician in his daily activity. The data in this system could easily be a part of a grand scheme to present a service that is simple to operate and does not consume time from the busy schedule of a practitioner.

The adverse reaction system could be classified according to a standardized glossary which would provide consistent data; for example:

a) country code; b) drug and drug category; c) manufacturer; d) suspected reaction with system effected; e) daily dose; f) method of administration; g) duration of administration; h) age; i) sex; j) race; k) diagnosis(es); l) previous treatment; m) concurrent therapy; n) laboratory data; and o) results (if any).

In a classical study conducted by Leighton Cluff, M.D.[3] it was pointed out that the greater number of adverse reactions observed occur with antimicrobial

agents and cardiac drugs. Hypnotics and sedatives were next, followed by antidiabetic agents and then antihypertensive compounds. He also stated that gastrointestinal reactions are most frequently observed. Neuromuscular reactions, metabolic, cardiovascular, cutaneous, hematologic, fever and multiple systems followed in that order. Pulomonary and miscellaneous types of reactions were least to be noted.

The implications of such a system are numerous, as many correlations can be identified, possibly leading to or directing research in new areas. Some reactions occur immediately while others may not occur for from 1 to 10 days. Gastrointestinal reactions are usually characterized by nausea and vomiting and diarrhea and have been noted more frequently in women. It has also been shown that reactions occur with greater frequency in white patients over 50 years of age than in blacks.[2,40,42,43]

The problem has therefore been presented and although it has many ramifications it does have a specific direction or end point. Information scientists should take an active lead in coordinating the masses of raw data and work in conjunction with the basic scientists and physicians to develop a program(s) that can collect, analyze, classify and disseminate functional information. If properly initiated it could become a part of the learning process for the next generation of physicians.

In summary, we have a problem involving many people who identify with drug development from varying viewpoints. They have a common goal of setting up a well structured and clearly defined system for adverse reaction collection. However, their approaches toward this objective vary. There is sufficient financial support for this project on the level of private industry

and the level of federal government's Health Education and Welfare Department. This objective will take a long time to reach but in the resolution of this problem there is a role for the information scientist to play in cooperation with the basic research scientist. The evaluation of this type of program will be an ongoing process and will continually need restructuring and reorganizing as additional data and analyses are completed.

NOTES

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